1643



# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Philip John Burke and Richard John Knox

Serial No.: 09/445, 865 Art Unit: 1642

Filed: February 11, 2000 Examiner: G. Nickol



For: *"THERAPEUTIC SYSTEMS"*

Assistant Commissioner for Patents
Washington, D.C. 20231

## APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 29, 31-33, 40 and 41 in the Office Action mailed October 2, 2001, in the above-identified patent application. A Notice of Appeal was mailed on January 31, 2002. The Commissioner is hereby authorized to charge Deposit Account No. 50-1868 $430.00 for the filing of this Appeal Brief with a one month extension of time. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

## (1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee Enzacta R & D Limited.

## (2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

## (3) STATUS OF CLAIMS ON APPEAL

Claims 1-40 are pending. Claims 29, 31-33, 40 and 41 are on appeal. Claims 1-29 and 34-39 are withdrawn as directed to a non-elected invention. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

## (4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment mailed July 10, 2001.

## (5) SUMMARY OF THE INVENTION

The claims are directed to a method of treating a human patient with a target cell to be destroyed wherein the target cell expresses an enzyme called NQO2 (page 45, lines 19-21). The method comprises the administration of (1) a prodrug, CB 1954, which is converted to a cytotoxic drug by the action of NQO2 and (2) the co-substrate for NQO2, NRH or an analogue thereof which can pass reducing equivalents to NQO2 (page 45, lines 21-24) (page 46, lines 7-9). The analogue may permeate the target cell membrane (page 46, lines 11-12). The patient may have cancer and the target cell may be a tumor which expresses NQO2 (page 47, lines 1-2; page 45, lines 26-27; claims 32, 40). The analogue of NRH may be 1-(carboxamidomethyl)-dihydronicotinamide (page 61, lines 1-20; claim 41). The method may further comprise determining before the administration of the prodrug or NRH or an analogue thereof, whether the target cells to be treated expresses NQO2 (page 48, lines 3-5; claim 33).

## (6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 29, 31-33, 40 and 41 are enabled as required by 35 U.S.C. § 112, first paragraph.

An outstanding issue is that of consideration of the prior art that has twice been submitted in an Information Disclosure Statement mailed April 28, 2000, and again by hand delivery on April 16, 2001, along with an additional reference, after the examiner stated he had not received copies of all of the publications. These references, having all been timely submitted originally and then re-submitted at the examiner's request prior to issuance of the office action from which this appeal follows, should have been considered and made of record. Enclosed are copies of the PTO 1449s and proof of receipt by the Patent Office.

## (7) GROUPING OF CLAIMS

The claims do not stand or fall together. The claims can be grouped as follows: (1) claim 29, (2) claim 31, (3) claim 32, (4) claim 33, (5) claim 40, and (6) claim 41. Claim 29 is directed to treating a patient with a prodrug which is converted to a cytotoxic drug by the action of NQO2, expressed by the targeted cell, and NRH or an analogue thereof which can pass reducing equivalents to NQO2, wherein the prodrug is CB 1954. Claim 31 is directed to defining the NRH analogue as being able to permeate the target cell membrane. Claim 32 is directed to defining the target cell as a tumor. Claim 33 is directed to a method of determining whether the target cell to be treated expresses NQO2, before administering the prodrug or NRH or analogue thereof. Claim 40 is directed to a patient having cancer. Claim 41 is directed to

defining the NRH analogue as being 1-(carboxamidomethyl)-dihydronicotinamide. Reasons for this grouping and arguments for the separate patentability of these groups of claims are provided below.

## (8) ARGUMENTS

### (a) The Claimed Invention

The present invention is related to the finding that human tumor cells can be killed by the administration of a prodrug, CB 1954, and the exogenous co-substrate, reduced niotinamide riboside or "NRH" or an analog thereof, for an enzyme, human NAD(P)H:quinone reductase 2 "NQO2". The prior art describes the administration of the prodrug, CB 1954, in combination with an enzyme, to kill tumor cells. See, for example, U.S. Patent No. 5,780,585 and U.S. Patent No. 5,958,682, which teach the use of an *E. coli* nitroreductase enzyme to activate CB 1954 for the treatment of human tumors. In contrast to the prior art which discloses the administration of an enzyme with the prodrug, appellants have discovered one can administer a prodrug along with an exogenous co-substrate for an enzyme, NQO2, which in combination with the co-substrate is able to convert the prodrug into a powerful cytotoxic compound.

Experiments in animals harboring tumors have shown that when a prodrug is specifically activated in the tumor environment, the animal is often cured of the cancer. The specificity of the treatment lies at the core of the efficacy of the treatment. The delivery of a cytotoxic agent specifically to tumor cells is highly desired. Normal cells are often killed when cytotoxic agents lack specific targeting or are administered systemically. There are many examples of using prodrugs which are selectively activated by enzymes present in tumors. The most familiar

example is gancyclovir, which is activated in the presence of thymidine kinase to yield a cytotoxic compound. Assuming that the prodrug is a good substrate for the enzyme specifically expressed in the tumor and that the difference in toxicity between prodrug and drug is a hundred-fold or more then, once a candidate enzyme has been identified, many classes of anti-cancer agent can often be derivatized to form appropriate prodrugs.

The presently claimed method is directed to a novel prodrug activation system in which the enzyme may be endogenous to human tumor cells. The co-substrate can be administered using standard methods of administration for most drugs. See, for example pages 47-52; also Figures 11 and 12, showing conversion of the prodrug in the presence of co-substrate to a cytotoxic compound, and Figures 15-18, showing the safety and non-toxicity of administration of the NRH co-substrate.

CB 1954 is an antitumor prodrug that is activated in certain rat tumors via its 4-hydroxylamine derivative to a potent bifunctional alkylating agent. Human tumor cells are normally unable to efficiently catalyze the conversion of CB 1954 to a cytotoxic agent via the human enzyme NQO1 which uses endogenous NAD(P)H as a co-substrate to reduce CB 1954. Human NQO1 does not appreciably convert CB 1954 into its cytotoxic form. However, another human enzyme has been discovered that can activate CB 1954, and it has been shown to be commonly present in human tumor cells. The enzyme is NQO2, but its activity is normally latent, and a nonbiogenic exogenous co-substrate such as NRH is required for enzymatic activity (see, for example, page 8, lines 18-21). This ternary system, including the cells to be killed, the

enzyme, NQO2, that the cells express, the prodrug CB 1954, and the exogenous co-substrate for the enzyme, NRH, is inactive if any one of the compounds is absent.

CB 1954 is a *proven* anti-tumor agent as defined by *in vivo* work in rats, in which CB 1954 is activated by the rat enzyme NQO1 (page 5, line 26 to page 7, line 16). Although NQO1 is present in human cells and is therefore an exploitable enzyme for inducing selective cytotoxicity as its levels are significantly raised (compared with the surrounding normal tissue) in tumor tissue, the human form of NQO1 metabolizes CB 1954 much less efficiently than rat NQO1 (Wu *et al.*, *Arch. Biochem. Biophys.*, 347:221-228, 1997). Thus, even those cells that are high in human NQO1 are insensitive to CB 1954, because there is inefficient conversion of CB 1954 to its toxic form. The catalytic difference between the two forms of the enzyme NQO1 (rat and human) is mainly accounted for by a single amino acid change at residue 104 (tyrosine in the rat enzyme and glutamine in the human enzyme). NQO2, which was identified on the basis of its homology to DT-diaphorase (NQO1), reacts with CB 1954 to produce the *identical* cytotoxic product as that produced by rat NQO1.

Accordingly, once one shows that in the presence of the appropriate exogenous co-substrate, NRH, the prodrug CB 1954 is converted by NQO2, an enzyme expressed in human tumor cells, into a cytotoxic drug, those skilled in the art would expect the claimed method to be effective, and would be enabled to use the method.

**(b) Rejections Under 35 U.S.C. § 112**

Claims 29, 31-33, 40 and 41 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

*i. The Legal Standard under 35 U.S.C. § 112, first paragraph*

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art,

the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

In this case, the examiner has not argued that one could not administer either the claimed prodrug CB 1954, nor the co-substrate, NRH, to a patient in need of treatment. The examiner has provided no support that one could not practice the claimed method. Rather, the examiner is actually making a utility rejection, under the guise of a section 112, lack of enablement, heading, knowing that the standard for utility has been met.

The standard under 35 U.S.C. 101, utility, has most recently been reviewed in the MPEP as follows. M.P.E.P. § 2107.01 clearly states that deficiencies under the "useful invention" requirement of 35 U.S.C. § 101 can occur when an applicant fails to identify any specific and substantial utility for the invention or fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the field of the invention. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966); *In re Ziegler*, 992 F.2d 1197, 26 USPQ2d 1600 (Fed. Cir. 1993). A second type of deficiency arises in the rare instance where an assertion of specific and substantial utility for the invention made by an applicant is not credible.

Therefore, absent a showing that one skilled in the art would not expect the claimed method to be efficacious, the examiner has failed to meet the burden under either 35 USC section 101 or 112, enablement. The examiner has provided no such support, only allegations that the examples, because they do not show efficacy in humans, do not demonstrate that the claimed method is enabled.

*ii. Factual Analysis of Claims 29, 31-33, and 40 under 35 U.S.C. § 112, first paragraph or under 101*

CB 1954 may be converted into a difunctional alkylating agent that has been demonstrated to have a dramatic and highly selective activity against the rat Walker 256 tumor, expressing NQO1, which is known to convert CB 1954 into a cytotoxic compound. These studies are outlined in the specification (see page 6 and Figure 1).

CB 1954 is not effective as a cytotoxic agent in the presence of the *human* form of NQO1. *Human* NQO1 does not appreciably convert CB 1954 into its cytotoxic form. Therefore, human tumors are not inherently resistant to CB 1954 in its cytotoxic form (page 6, line 24 to page 7, line 4 of the present specification) but are not killed by CB 1954 alone due to the inefficiency of the endogenous NQO1 enzyme. However, one of ordinary skill in the art will appreciate that the initial activation of CB 1954 by human NQO2, in the presence of an *exogenous* co-substrate (i.e. NRH), leads to a hydroxylamine intermediate (see Figure 3 of the present specification) which is identical to the hydroxylamine intermediate produced by the activation of NQO1, in the presence of an *endogenous* co-substrate (i.e. NAD(P)H), though not by the same mechanism (see Figure 1 of the present specification). Therefore, one skilled in the

art would have every expectation that administration of the prodrug and the exogenous co-substrate NRH would lead to production of cytotoxic compound.

It is well accepted in the art that reduction of CB 1954 to its 4-hydroxylamine derivative can lead to an anti-tumor effect irrespective of the enzyme involved (page 6, lines 12-22 of the present application). Indeed, U.S. Patent No. 5,780,585 and U.S. Patent No. 5,958,682 referenced above teach the use of an *E. coli* nitroreductase enzyme to activate CB 1954 for the treatment of human tumors. Nitroreductase has been used in gene targeting assays (gene directed enzyme prodrug therapy and antibody directed enzyme prodrug therapy) because it reduces CB 1954 much more rapidly than rat NQO1, although forming an equal mixture of the 2- and 4-hydroxylamines (the 2-hydroxylamine is less toxic than the corresponding 4-derivative, but still more cytotoxic than CB 1954 itself). NQO2 resembles rat NQO1 in that, unlike the bacterial enzyme, it forms only the more cytotoxic 4-hydroxylamine reduction product of CB 1954. Rat NQO1, in the presence of a co-substrate, activates CB 1954 *in vivo* to produce an effective anti-tumor agent. One of ordinary skill in the art would realize that activation of CB 1954 by administration of an exogenous co-substrate with the prodrug, as presently claimed, would be effective in the treatment of human tumors.

Example 8 of the present specification demonstrates the potentiation of CB 1954 in human glioblastoma cells in the presence of NQO2 co-substrates. These glioblastoma cells were *not* transfected with NQO2 in these experiments. The prodrug CB 1954 was exposed to levels of NQO2 occurring *naturally* in the cell line, in combination with exogenous substrate.

It is acknowledged that human NQO2 is *not* the same enzyme as NQO1. If human cells expressed an NQO1 that was able to convert the prodrug to a cytotoxic compound in human cells, there would be no need of the claimed method. However, what appellants have discovered is that human cells express a different enzyme, NQO2, which, when an exogenous co-substrate is administered to the cells, is effective in converting the prodrug to a cytotoxic compound, the same cytotoxic compound as shown to be produced by the action of the rat NQO1 enzyme utilizing endogenous substrate. See Table 1 on page 57 of the originally filed specification. Table 1 demonstrates that human NQO2 in the presence of an NRH co-substrate reduces CB 1954 six hundred times faster than human NQO1 and a hundred times faster than rat NQO1. The actual cytotoxic compound responsible for the cytotoxic effect *is the same* as that shown to elicit the effect in response to rat NQO1.

The appellants have not extrapolated the efficacy of the resultant cytotoxic compound from *in vitro* studies. The appellants submit that in paper 12 (Response and amendment to the Office Action mailed on April 10, 2001), page 5 (second paragraph), the statement referring to examples being used "as a way to illustrate that the administration of co-substrates *to living cells* is achievable...." (emphasis added), does not reflect upon the administration of co-substrates *in vitro*. The efficacy of the resultant cytotoxic compound (i.e. CB 1954), has been demonstrated not only in cells *in vitro* but also based on the above-mentioned rat *in vivo* studies. Accordingly, one skilled in the art would be enabled to use the claimed method, with an expectation that it would be effective in producing a cytotoxic compound from the prodrug CB 1954.

*iii. The Examiner has completely failed to individually examine the dependent claims.*

It is well established that each claim must be separately examined for patentability. It is not enough, as here, to look at a single independent claim and reject all claims. No rationale has been presented as to why the subject matter of claim 31, where the NRH analogue is able to permeate the cell membrane, is not enabled by the specification. Furthermore, no rationale has been provided as to why the NRH analog 1-(carboxamidomethyl)-dihydronicotinamide is not enabled as a reducing agent to be utilized in a reaction converting CB 1954 to a toxic agent.

No argument has been made as to why the method comprising determining whether the target cell to be treated expresses NQO2 before the administration of the prodrug or NRH or an analogue thereof, to the patient, is not enabled. Lastly, no argument has been made as to why the specification is not enabling for treating a cancer patient with the claimed method, or for targeting a tumor cell.

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112,

first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

*Id.* at § 2164.05 (emphasis added).

In this case, the examiner is relying on conclusory statements without putting forth specific reasons describing why the claims are not enabled by the specification. The patent examiner cannot just assert that the application is not enabled. As stated in In re Marzocchi at 439 F.2d 220 (CCPA 1971:

[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made [, enablement under § 112, first paragraph], to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure **and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement**. Otherwise, there would be no need for the Appellant to go to the trouble and expense of supporting his presumptively accurate disclosure.

*Id.* at 224.

The MPEP instructs examiners to make specific findings of *facts* to rebut Appellants' presumption and "specifically identify what information is missing and why one of skill in the art could not supply the information without undue experimentation." MPEP at § 2164.05. The examiner should provide references to support a *prima facie* case of lack of enablement. *Id.*

The Examiner has failed to meet the legal burden in this case.

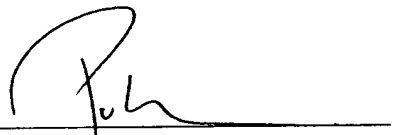
## (9) SUMMARY AND CONCLUSION

The appellants have shown that human enzyme NQO2 exists that in the presence of an exogenous NRH co-substrate can convert the prodrug CB 1954 to a cytotoxic compound for use in a simple but selective antitumor therapy. It is clear that the mechanism of action of CB 1954 is fully understood and it is accepted that its lack of activity against human tumors is due to the very inefficient conversion of CB 1954 to its active form by the human enzyme NQO1. The appellants have described a method of overcoming this fundamental limitation - add an exogenous co-substrate for a separate and distinct enzyme, NQO2, which is then able to convert the CB 1954 to a cytotoxic compound. There is no reason to suggest that CB 1954, activated using the disclosed method, should be less effective as an anti-tumor agent than CB 1954 activated by any other method (for example, as in rats where it is a proven anti-tumor agent).

As provided in the foregoing discussion, four salient points need to be reiterated: (1) the cytotoxic form of CB 1954 is identical regardless of the converting enzyme; (2) the 4-hydroxylamine intermediate that is formed during this conversion reaction is identical in reactions governed by NQO1 or NQO2: (3) rat NQO1, in the presence of an endogenous co-substrate, activates CB 1954 *in vivo* to produce an effective anti-tumor agent (reviewed in Knox *et al.*, *Cancer Metastasis Rev.*, 1993); and (4) NQO2 in the presence of an exogenous co-substrate (NRH) activated CB 1954 *in vitro* to selectively kill human tumor cells. Therefore one skilled in the art would predict that the claimed method would be effective in treating humans.

For the foregoing reasons, the Appellant submits that the claims 29, 31-33, 40 and 41 are patentable.

Respectfully submitted,



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## Appendix: Claims On Appeal

1. A compound comprising a target cell-specific portion and human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof which has substantially the same activity as NQO2 towards a given prodrug, or a polynucleotide encoding said NQO2 or said variant or fragment or fusion or derivative.

2. (Amended) A compound according to [C]claim 1 comprising a target cell-specific portion and human NAD(P)H:quinone reductase 2 (NQO2).

3. (Amended) A compound according to [Claim 1 or 2] claim 1 wherein the target cell-specific portion is tumour cell-specific.

4. (Amended) A compound according to [any one of Claims 1 to 3] claim 1 wherein the target cell-specific portion comprises an antibody or fragment or derivative.

5. (Amended) A compound according to [any one of Claims 1 to 3] claim 1 wherein the target cell-specific portion comprises a macromolecule.

6. (Amended) A compound according to [any one of Claims 1 to 5] claim 1 wherein the human NAD(P)H:quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof is capable of being located substantially inside or following expression of the polynucleotide is located substantially inside the target cell.

7. (Amended) A compound according to [any one of Claims 1 to 6] claim 1 comprising means for delivering said polynucleotide to said target cell.

8. A recombinant polynucleotide comprising a target cell-specific promoter operably linked to a polynucleotide encoding human NAD(P)(H):quinone reductase 2 (NQO2) or a variant or fragment or fusion or derivative thereof which has substantially the same activity as NQO2 towards a given prodrug.

9. (Amended) A recombinant polynucleotide according to [C]claim 8 wherein said promoter is tumour cell-specific.

10. (Amended) A recombinant polynucleotide according to [C]claim 8 [or 9] comprising a polynucleotide encoding NQO2.

11. (Amended) A recombinant polynucleotide according to [any one of Claims 8 to 10] claim 8 which is capable, following expression in a target cell, of providing the NQO2 or a variant or fragment or fusion or derivative thereof located substantially inside the target cell.

12. (Amended) A compound according to [any one of Claims 1 to 7] claim 1 wherein said polynucleotide is the recombinant polynucleotide of [any one of Claims 8 to 11] claim 8.

13. (Amended) A therapeutic system comprising a compound according to [any one of Claims 1 to 7 or 12] claim 1, or a polynucleotide according to [any one of Claims 8 to 11] claim 8 and a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

14. (Amended) A system according to [C]claim 13 wherein the prodrug is CB 1954 or an analogue thereof.

15. (Amended) A system according to [C]claim 14 wherein the prodrug is CB 1954.

16. (Amended) A system according to [any one of Claims 13 to 15] claim 13 further comprising a cosubstrate for NQO2.

17. (Amended) A system according to [C]claim 16 wherein the cosubstrate is nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

18. (Amended) A method of treating a patient with a target cell to be destroyed the method comprising (a) administering to the patient a compound according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 11] claim 8; (b) allowing the NQO2 or a variant or fragment or fusion or derivative thereof to localize at, or be expressed in, the target cell; and (c) administering a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

19. (Amended) A method according to [C]claim 18 wherein the patient has a tumour to be treated.

20. (Amended) A method according to [C]claim 18 [or 19] wherein the prodrug is CB 1954 or an analogue thereof.

21. (Amended) A method according to [C]claim 20 wherein the prodrug is CB 1954.

22. (Amended) A method according to [any one of Claims 18 to 21] claim 18 the method further comprising administering to the patient a cosubstrate for NQO2.

23. (Amended) A method according to [C]claim 22 wherein the cosubstrate is nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

24. (Amended) A compound according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 10] claim 8, for use in medicine.

25. (Amended) Use of a compound according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 11] claim 8, in the manufacture of a medicament for treating a patient with a target cell to be destroyed.

26. (Amended) Use as defined in [C]claim 25 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

27. (Amended) Use of a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 in the manufacture of a medicament for treating a patient with a target cell to be destroyed wherein the patient has been, is being or will be administered a compound according to [any one of Claims 1 to 7 or 12] claim 1, or a recombinant polynucleotide according to [any one of Claims 8 to 11] claim 8.

28. (Amended) Use as defined in [C]claim 27 wherein the patient has a tumour to be treated.

29. (Amended) A method of treating a human patient with a target cell to be destroyed wherein the target cell expresses NQO2 the method comprising administering to the patient a prodrug which is converted to a cytotoxic drug by the action of NQO2 and nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2, wherein the prodrug is CB 1954.

31. (Amended) The method of claim 29 wherein the analogue of NRH is able to permeate the target cell membrane.

32. (Amended) The method of claim 29 wherein the target cell is a tumour.

33. (Amended) The method of claim 29 the method further comprising determining, before administering the prodrug or NRH or an analogue thereof, whether the target cell to be treated expresses NQO2.

34. A therapeutic system comprising a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 and nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

35. Nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2 for use in medicine.

36. Use of nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2 in the manufacture of a medicament for treating a human patient with a target cell to be destroyed.

37. (Amended) Use as defined in [C]claim 36 wherein the patient has been, is being or will be administered a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2.

38. Use of a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 in the manufacture of a medicament for treating a human patient with a target cell to be destroyed wherein the patient has been, is being or will be administered NRH or an analogue thereof which can pass reducing equivalents to NQO2.

39. A kit of parts comprising a means for determining whether a target cell to be treated expresses NQO2 and NRH or an analogue thereof which can pass reducing equivalents to NQO2.

40. The method of claim 29 wherein the patient has cancer.

41. The method of claim 29, wherein the analogue of NRH is 1-(carboxamidomethyl)-dihydronicotinamide.

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Serial & Docket No.: 09/445,865
Filed: February 11, 2000

## CERTIFICATE OF TRANSMISSION UNDER 37 CFR 1.8

I hereby certify that an Appeal Brief (in triplicate) with Certificate of Transmission Via Facsimile Under 37 C.F.R. § 1.8; Fee Transmittal Sheet (in duplicate); Transmittal Form; copy of filed stamped post-card with a copy of the IDS submitted on April 29, 2000; a copy of the Certificate of Hand Delivery on April 17, 2001 and copy of the Supplemental IDS; authorization to charge/credit Deposit Account No. 50-1868, along with any paper referred to as enclosed, is being transmitted via facsimile to **TC 1600** at **(703) 872-9306** within the United States, to the Commissioner for Patents, Washington, D.C. 20231 on the date shown below.

Aisha Wyatt

Date: April 30, 2002

ATL1 #515781 v1

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| Applicant: | Phillip John Burke and Richard John Knox | | |
| Serial No.: | 09/445, 865 | Art Unit: | 1642 |
| Filed: | February 11, 2000 | Examiner: | G. Nickol |
| For: | *"THERAPEUTIC SYSTEMS"* | | |

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| Applicant: | Phillip John Burke and Richard John Knox | | |
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